REMARKS

Claims 1-4 and 6 – 24 were examined in the present Office Action.

First, Applicants thank the Examiner for withdrawal of certain of the previous grounds of rejection under § 35 U.S.C. 112, first paragraph, in view of Applicants amendments and remarks. Specifically, the rejection of claims 12-20 for lack of enablement and of claims 1-4 and 6-20 for lack of adequate were withdrawn.

Remaining rejections, which are discussed below, concerned claims 1-4 and 6-23 (lack of enablement) and claims 1-4 and 21-24 (obviousness).

The Office Action has been carefully studied. Applicants thank the examiner and his supervisors for considering claims (and comments) submitted on January 30, 2008, for discussion only (not for entry into the record).

The Examiner responded orally to the undersigned with the Office's view of those claims and arguments in connection with the present rejections. Those comments were summarized in the Interview Summary Record dated March 6, 2008 which is further discussed below. Applicants were given to understand that the nature of the proposed amendments were such that the Office would not enter them after the pending final rejection. For this reason Applicants have decided to file an RCE in order to ensure entry of their claims and remarks and full examination.

The following main amendments have been made to the claims in light of the Examiner's suggestions and indications in the Interview Summary record.

1. The scope of all claims (1, 7 and 10) that were directed to sequences with at least 70% identity to SEQ ID NO:1 have been narrowed to at least 95% sequence identity.

2. Claim 10 has been rewritten as an independent claim, emphasizing that a cell that has the ability to produce one of several fermentation products (lactic acid, acetic, acid, succinic acid, amino acids, 1,3-propane diol, ethylene, glycerol., a β lactam antibiotic or cephalosporin) as a result of its expression of one or more enzymes is also transformed with an expression construct encoding a xylose isomerase (with the same properties as in claim 1) so that the cell can now directly isomerize xylose to xylulose as well as having improved production of the classes of fermentation product listed above.

3. Claims 21-23 are cancelled (and the 9%% identify limitation of claim 23 imported into claim 1.

4. Various other amendments are made to improve the clarify of the language.

5. New claims 25-28 are added. Claims 25, 27 and 28 limit the scope of claims 1, 7, and 10, respectively, to a naturally occurring eukaryotic xylose isomerase, Claim 26 narrows the scope of claim 7 to a xylose isomerase with SEQ ID NO:1

None of the amendments or new claims introduce new matter. Support for the amendment of claim 1 can be found at least at page 7, lines 6-11, original claim 5 and in the paragraph bridging pages 7 and 8. Other amendments are supported by the original claims or throughout the specification

Entry of these amendments and consideration of the Remarks below are respectfully requested. Applicants believe that the claims are now in condition for allowance.

I. Rejections for Lack of Enablement under 35 U.S.C. §112, 1st Paragraph

Claims 1-4 and 6-23 were rejected under 35 U.S.C. 112, first paragraph, due to lack of enablement. According to the Office, specification does enable a cultured isolated eukaryotic cell transformed with a nucleic acid construct comprising a nucleotide sequence encoding a xylose isomerase comprising the amino acid sequence of SEQ ID NO: 1; and a process for producing ethanol, lactic acid, acetic acid, succinic acid, an amino acid, 1,3-propanediol, ethylene, glycerol, a β-lactam, or cephalosporin comprising fermenting a medium containing a source of xylose with the eukaryotic cell. However, the specification allegedly does not enable the other embodiments recited in the claims. Applicants arguments filed September 11, 2007, were not found persuasive.

The Action asserted that the nature and breadth of the amended claims encompass any cultured eukaryotic host cell transformed with any nucleic acid construct comprising any nucleotide sequence encoding any xylose isomerase comprising an amino acid sequence that is at least 70% identical to SEQ ID NO:1. According to the Office (as set forth in both the Office Action and the Interview Summary), although later-discovered amino acid sequences of xylose isomerases described in WO04/99381 and WO 06/009434 had 97% and 83% identity to SEQ ID NO:1, respectively, this would not provide adequate guidance and predictability altering SEQ ID NO:1 and maintaining the xylose isomerase activity. The Summary noted, however, that claims in which the xylose isomerase was at least 95% identical to SEQ ID NO:1, would be enabled by the specification.

The Action further noted that the specification **does** not provide guidance, working examples, or a basis for predicting how to make the genetic modifications recited in claims 7-11.

Applicants' Response

While Applicants continue to disagree with the foregoing analysis, in order to advance prosecution, they have now narrowed the following Claims 1, 7, 10 directly to recite this limitation of 95% (while the other claims (such as 8, 9 and 11) include this limitation by virtue of their dependence). Further, dependent claims 8- 9 11 have been amended in various ways to clarify their language which also contributes further to their adequacy under § 112, first paragraph.

New Claims 25, 27 and 28 respectively limit claims 1, 7 and 10 (which are already limited to a xylose isomerase at least 95% identical to SEQ ID NO:1) to "naturally occurring" xylose isomerases. This is supported in the specification, *e.g.*, at page 8, lines 11-23. as one would not have to induce alterations in SEQ ID NO:1, but rather, to look to existing sequences that have the requisite enzymatic activity in their natural host, and that have at least 95% identity with SEQ ID NO:1. Routine experimentation will tell whether these sequences will function in accordance with the claim language and confer the indicated phenotype on the cell.

As for the Office Action's specific indication that claim 7-11 are not enabled with regard to the additional genetic modifications, the Office appears to be reading claim 7 as requiring that Applicants' transformed cells (of claim 1) be further modified with genes conferring the listed properties. First, claim 7 was amended to independent format to emphasize that cells with such properties are known in the art (see specification at page 10, line 23 - page 11, line 7) discussing various of these genes and citing literature for guidance regarding these modifications. Specifically, the review paper by Zaldivar *et al.* (of record) provides much of this type of support (as of 2001). These references discuss ways to promote fermentation of xylose by exploiting properties other than xylose isomerase (*as listed in claim 7).* These modifications have already been made in the prior art as indicated in the cited section of the specification. In amended claim 7, applicants are adding to these cells the xylose isomerase-encoding DNA (as that recited in claim 1) to express a particular xylose isomerase and thereby confer on these cells, the ability to directly isomerize xylose to xylulose. Applicants believe that no further guidance would be necessary to enable claims 7-11 as amended, because their invention is not directed to these known genes, or cells that have been genetically modified to possess the listed 6 properties, that confer certain advantageous properties on such cells. Rather, what is claimed here are cells that further comprise and express the particular xylose isomerase coding sequence which confers an additional advantageous phenotype to the cell.

As indicated in the Interview Summary, Applicants could overcome the enablement issue as concerns claim 7 *et seq.* by introducing the limitation that the host cells are transformed with a nucleic acid expression construct comprising a nucleotide sequence encoding a xylose isomerase having at least 95% identity to SEQ ID NO:1. The claims indeed have been amended in this manner.

In view of the amendments and the foregoing remarks, it is believed that all the present claims comply with §112/first paragraph, so that the rejection for lack of enablement may properly be withdrawn.

II. Rejection Under 35 U.S.C. 103(a)

The Applicant maintained the ejections of Claims 1-4 and 21-24 as being obvious over the same three references as before:

(i) Guan in view of Accession No. Q9P8C9; or

(ii) Karlsson in view of in view of Accession No. Q9P8C9

To reiterate certain aspects of the rejections,

A. Accession Q9P8C9 teach a xylose isomerase having an amino acid sequence that is (100%) **identical** to SEQ ID NO: 1, *i.e.,* the xylose isomerase sequence used in the present invention.

B. Guan is said to teach

(1) expression vectors with promoters.

(2) prokaryotic host cells (such as *E. coli*).

(3) eukaryotic host cells (such as yeast.

(4) methods for making, expressing, isolating, and purifying any protein fused to the *E. coli* maltose binding protein (MBP) using (1), (2) or (3); and

(5) that these products and methods are useful for purifying virtually any hybrid polypeptide molecule employing recombinant techniques.

Admittedly, there is no teaching in Guan of yeast cells transformed with a polynucleotide encoding a xylose isomerase comprising an amino acid sequence that is SEQ ID NO: 1 or that has at least 95% identity to SEQ ID NO: 1.

Karlsson is said to teach filamentous fungus *Trichoderma reesei* host cells transformed with an expression vector containing a polynucleotide encoding Ce161A (EG IV). Admittedly, there is no teaching in Guan of *Trichoderma reesei* cells transformed with a polynucleotide encoding a xylose isomerase comprising an amino acid sequence that is SEQ ID NO: 1 or that has at least 95% identity to SEQ ID NO: 1.

The Office concluded that it would have been *prima facie* obvious to transform yeast cells (Guan) or *Trichoderma reesei* cells (Karlsson) with the polynuc1eotide encoding the xylose isomerase of SEQ ID NO:1 (Accession Q9P8C9). The **motivation** to do this allegedly comes from a generalized motivation to **express and purify** the xylose isomerase (SEQ ID NO:1). The well-developed state of recombinant techniques for heterologous or homologous expression of proteins in the art was allegedly the basis for there being a reasonable expectation for success.

C. Office's Response Applicants' Prior Arguments

The Office did not find Applicants' arguments persuasive, as Applicants allegedly attacked the references "individually" where the rejections are based on combinations. The Action went on to recognize the requirement that there be a teaching, suggestion, or motivation to do combine the references, either in the references themselves or in the knowledge generally available to one of ordinary skill. The Office noted that the claims as written did not specifically exclude recombinant protein expression. Thus, one of ordinary skill in the art would have been motivated to combine Guan or Karlsson with Accession Q9P8C9 to express and purify the xylose isomerase taught by Accession Q9P8C9.

The Office cited In re Kahn for the proposition that "it is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant.

The Action rebutted Applicant's argument that the Office relied upon improper hindsight reasoning, citing *In re McLaughlin,* 170 USPQ 209 (CCPA 1971) and stating that

> ...any judgment on obviousness is, in a sense, necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge available to those of ordinary skill (at the time the invention was made), and does not include knowledge gleaned only from the applicant's disclosure, such reconstruction is proper...

D. Examiner's Comments in the Interview Summary

In Applicants "talking points" (not submitted for entry), they raised the notion that most of the available xylose isomerases for which expression in yeast had been attempted, had failed. The Examiner responded this argument would be considered with an appropriate Declaration.

The Summary also indicated that amending the claims to recite that the claimed host cell is transformed with a nucleic acid expression construct comprising a nucleotide sequence encoding a xylose isomerase having 95% identity to SEQ ID NO:1 would aid in overcoming the obviousness rejections of record.

E. Applicants' Response

Applicants note at the outset that in view of the cancellation of claims 21-23, the rejection is moot as to those claims. The limitation of claim 23 was imported into claim 1, and claim 24 remains unchanged, so Applicants will treat this rejection as now being directed to claims 1-4 and 24 and new claim 25.

Claims1-4, as amended are directed to host cells (and not to methods for isolating and purifying a particular protein), as follows:

(a) a cultured eukaryotic host cell transformed with a xylose isomerase gene encoding a protein that is at least 95% identical to SEQ ID NO:1 (claim 1) or identical to SEQ ID NO:1 (claim 24);

(b) the eukaryotic cell is a yeast cell (claim 2);

(c) the yeast cell is a member of one of nine indicated species (claim 3);

(d) the eukaryotic cell is a filamentous fungus (claim 14).

Claim 18, in which the yeast cell is recited as being a member of one of nine yeast genera, and from which claim 3 depends, was not included in this rejection. In case this was an oversight on the Office's part, Applicants believe their remarks below, directed primarily to claims 1 and 24, equally support the non-obviousness of claim 18.

Applicants incorporate here the discussion of the legal test for obviousness set forth in the their prior Response.

Suggestion or Motivation

Applicants also draw the Examiner's attention to the **de Bont Declaration** submitted herewith, primarily in support of Applicant's position that the Office has not met its burden in showing that there would have been motivation to combine the Guan or the Karlsson reference with the disclosure of SEQ ID NO:1 as a Piromyces sp. Strain E2 xylose isomerase protein.

As stated by Dr. de Bont, and as touched upon in Applicants' previous response, several dozen xylose isomerase sequences were known at the time this invention was made, a number of which were provided in Harhangi, HR *et al.*, 2003, (of record), Fig. 4A. There are more than 1500 xylose isomerases sequences (partial) currently available. The present invention (as set forth in claim 1 is directed to a transformed eukaryotic cell that has been transformed to express a xylose isomerases that has at least 95 % identity with SEQ ID NO:1), which confers on the cell the ability to directly isomerize xylose to xylulose. **The Office has not provided any specific motivation** for choosing any particular xylose isomerase, let alone SEQ ID NO:1 or homologues

with at least 95% sequence identity, from among the many available xylose isomerase sequences.

Rather the Office has relied upon what can be characterized as a "general desire in the art" to isolate and express a particular protein. It is only the disclosure of the present invention that has provided a motivation for selecting a particular xylose isomerase for transforming the cells. Applicants understand the notion, expressed in the Office Action, that an obviousness rejection by definition, involves hindsight. If that is so, why has the CCPA and the Federal Circuit gone to lengths to warn against the insidiousness of using Applicants disclosure to pick and choose among references to reconstruct an applicant's invention. For example, the Federal Circuit has recognized the extreme ease, yet mistaken reasoning, of using hindsight in determining that an Applicant's own invention can be adduced from various sources and that this would be obvious to one skilled in the art. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F2d. 1540, 220 U.S.P.Q. 303 (Fed. Cir. 1983) *cert. denied*, 469 U.S. 851 (1984). The *Gore* Court specifically stated:

> To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior reference or references of record convey or suggest that knowledge is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against the teacher.

(emphasis added).

Applicants have already stated, citing from *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143 (Fed. Cir. 1985) in the prior Response, that"[w]hen prior art references require selective combination by the court to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself." Nothing in the cited prior art here or the Office's analysis provides such a reason.

> ...[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. This requirement is as much rooted in the Administrative Procedure Act [for our review of Board determinations], which ensures due process and non-arbitrary decision-making, as it is in § 103.

In re Kahn, 441 F.3d 977, 985 (Fed. Cir. 2006)441 F.3d at 987-88 (quoting *In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000)) (citations omitted)

First, in analyzing Guan, one cannot escape the fact that this reference deals in a limited way with a prokaryotic or eukaryotic expression system in which DNA encoding protein X to be expressed is fused to DNA encoding the maltose binding protein (MBP), a "label" that can serve as a "handle" for isolation of the X-MBP fusion polypeptide. There is no suggestion or motivation here to insert a gene encoding a particular enzyme, here xylose isomerase, to confer on the transformed cells a ne enzymatic activity (isomerization of xylose to xylulose) which is at

the heart of the present invention. There would be no benefit, and likely disadvantages, to fusing xylose isomerase encoding DNA of the claimed scope to MBP (or any other similar "technological handle" protein) to provide the phenotypic change featured in the rejected claims.

Second, Karlsson deals with the transformation of *Trichoderma reesei* cells with an *endogenous* cellulase gene for producing/purifying the cellulase enzyme. There is no suggestion or motivation here to insert any other gene from another cell, *a fortiori* a xylose isomerase, that will confer a new phenotype on the cell, that of isomerizing xylose to xylulose.

The presently rejected claims have now been narrowed to transformed cells expressing a particular sequence (SEQ ID NO:1) or one having at leas 95% identity with it. The motivation to chose any sequence diminishes as the % identity of the sequence increases because the motivation to chose a specific sequence or a subpopulation of sequences from a larger population of possible sequence is inversely related to the size of the subpopulation. The rejection and cited references does not provide motivation to select any particular xylose isomerase sequence or sequences to provide the recited properties on the cells.

Therefore, Applicants believe that the cited art does not provide the requisite motivation for a legally sufficient *prima facie* obviousness rejection . For this reason alone, such a rejection against the amended claims would not be proper.

Expectation of Success

Applicants also contend, and the de Bont Declaration supports, that the cited references do not meet the burden of the "expectation of success" arm of the obviousness test. As Dr. de Bont notes, the specification explains on page 2, line 26 to page 3, line 10, that most of the available xylose isomerase sequences for which expression in yeast had been attempted failed to produce active xylose isomerase. Initially, when expressed in yeast, the only successful xylose isomerase came from a rather *unexpected source* - certain thermophilic bacteria. Dr. de Bont states that at suitable growth temperatures for yeast, this thermophilic xylose isomerase would not have not sufficient activity to support the phenotypic change in the yeast required by the claim language. Dr. de Bont also emphasized that SEQ ID NO:1 is "more similar to some of the bacterial proteins (*Bacillus*) that **failed the test** of active expression in yeast than to the enzyme from these thermophilic bacteria." This led to his conclusions, as an expert skilled in this art, he would not have reasonably expected success in expressing the claimed xylose isomerase in active form in a yeast or a fungus so that it would confer on the cell the ability to directly isomerize xylose to xylulose (and thereby permit the cells to grow on xylose as a sole carbon source).

For the reasons indicated above, and further in view of the amendments to the claims, Applicants believe that it would be proper to withdraw the above rejections under § 103(a) and respectfully requests the Office to do so.

III. CONCLUSION

In conclusion, it is respectfully requested that the above amendments, remarks and requests be considered and entered. Applicants request that the currently presented claims, including amended and new claims, be allowed.

If the Examiner deems it helpful, he is requested to phone the undersigned at the phone number shown below to discuss the present amendments and response.

Respectfully submitted,

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